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## Editorial

## Long-term outcome after interferon therapy in patients with chronic hepatitis C.

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Hepatitis C Virus (HCV) infects between 170 and 350 million people worldwide and is currently the leading indication for liver transplantation in Europe and the United States.

HCV persists indefinitely in most infected patients, leading to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. The overall prevalence of anti HCV in Europe and the United States is less than 2%.<sup>1-3</sup>

Therapy for hepatitis C has advanced in the last 25 years. Even before the discovery of HCV, some studies demonstrated that therapy with interferon alfa induced clinical and histological remissions in a proportion of patients with chronic non-A, non-B hepatitis.<sup>4</sup> Subsequently, a series of randomized clinical trials confirmed the efficacy of interferon as therapy for chronic hepatitis C. This led to the development of the concept of sustained virological response. Sustained virological response (SVR) is defined by undetectable serum HCV RNA using a sensitive PCR assay, six months after ending therapy. With the current standard combination therapy using peginterferon alfa plus ribavirin, SVR is achieved in 54 to 63% of treatment naive patients, depending on HCV genotype, ribavirin dose and therapy duration. Patients infected with genotype 2 and 3 achieved a higher SVR than patients infected with genotype 1.<sup>5-7</sup>

Patients who achieve SVR have been included in long-term follow-up studies that have shown that SVR appears to be a durable clinical end-point. These follow-up studies have shown that less than 4% of patients who achieve a SVR will relapse within 5-6 years of follow-up.<sup>8</sup> This high SVR rate is the same, independently of the type of interferon based therapy, monotherapy with interferon, combination therapy with standard interferon and ribavirin or combination therapy with pegylated interferon and ribavirin. Both peginterferon alfa 2b and alfa 2a combined with ribavirin have demonstrated that SVR

persists after 5 years of follow-up. In addition, small series follow-up for more than 10 years show similar results in terms of persistence of SVR. In addition to viral clearance, liver enzymes remains persistently normal and liver histology has been shown to improve or remain unchanged in the majority of patients who achieved SVR. The long-term outcome for those patients is excellent.

Over the last few years, a new concept has introduced the possibility that SVR may indicate cure. One of the first papers supporting this concept was published by Lau and coworkers who followed the initial 10 patients with chronic non A non B hepatitis treated at the National Institute of Health (NIH) for 10 years.<sup>9</sup> They evaluated the long term clinical, histological and virological outcome of these patients treated with interferon alfa2b for 6 weeks. Among them, 5 achieved SVR after therapy and all remained HCV RNA negative at the last follow-up. Liver biopsy specimens were not reactive for HCV RNA, and all the patients showed improvement in both inflammation and fibrosis and were either normal or had mild, nonspecific changes. These findings suggested that interferon alfa therapy eradicated HCV infection and that these patients were cured of chronic hepatitis C. Other recent works have also demonstrated SVR to be associated with considerable benefits, including improvement in liver function test findings, improvement in liver histology, decreased infectivity, loss of HCV RNA from the liver, improvement in quality of life and improvement in survival.<sup>10-13</sup> All of these results have allowed the EMEA to accept the term «cure» for patients who achieve SVR, which means that HCV is currently a curable disease.

There is a small percentage of late HCV relapses among patients who remained HCV RNA negative during the first six months after therapy discontinuation, which could be explained by different factors.<sup>14-16</sup> One explanation is the type of HCV assays used to detect HCV RNA. A very sensitive PCR assays with a lower limit of detection of approximately 50 IU/mL is needed to assure SVR. The use of a less sensitive HCV RNA assay could misinterpret the results and make a mistake between a true non response and a relapse. Another possible explanation, particularly for the occurrence of late relapse despite lack of HCV RNA six months after stopping therapy, is reinfection caused by repeat exposure to hepatitis C, a factor which should especially be consid-

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ered in intravenous drug users. A third explanation is HCV persistence at very low levels. Two studies have shown, using a highly sensitive RT PCR assay, the presence of residual HCV RNA in small number of individuals up to 5 years after apparent spontaneous or treatment induced viral clearance. In addition to sera, HCV RNA was detected in peripheral blood mononuclear cells (PBMC), and in dendritic cells. Importantly, after mitogen stimulation of PBMC, the negative strand (a replicative intermediate) of HCV RNA was detected in 75% of cases, suggesting ongoing viral replication and also in liver tissue. In a large study among 400 patients with SVR, 98% had undetectable hepatic HCV RNA, while only 2% (7 patients) had detectable hepatic HCV RNA. Five of them have been followed and 2 had reappearance of serum HCV RNA 12 months after therapy. The significance of these low levels of HCV RNA is still unclear and seems not to be associated with a progressive liver disease.

However, in spite of effective therapy, the prevalence of hepatocellular carcinoma (HCC) has increased in Western countries and currently HCV cirrhosis is the most common cause of liver transplantation worldwide.<sup>17</sup> Studies projecting future complications of chronic hepatitis C, using mathematical models, are not optimistic.<sup>18,19</sup> A lot of currently asymptomatic patients infected with HCV will progress to liver cirrhosis and HCC in the coming years, and the number of cases of liver related deaths will increase. Antiviral therapy for patients with chronic hepatitis C has the final objective of decreasing the mortality of infected patients, preventing HCC and decompensation of liver cirrhosis. The efficacy of therapy in patients with SVR has shown that liver fibrosis diminishes when the inflammatory activity disappears, probably due to the antifibrogenic effect of interferon. It is important to note that even in patients without a sustained virologic response, liver histology can improve by stopping the progression of fibrosis.<sup>20</sup>

In this setting, there are some important and difficult to answer questions such as whether antiviral therapy can prevent the development of HCC in patients with advanced liver disease and whether therapy might be beneficial in non-responders.

Regarding the first question, there are several studies with heterogeneous designs, some randomized, non-randomized, usually with a small number of patients and the majority of them published in Japan, showing in many of them a decrease in the number of HCC cases in patients with cirrhosis due to HCV treated with interferon vs. untreated controls.<sup>21-22</sup> However, the high rate of HCC in the control group made the results doubtful. In 1998, data from 2,890 patients, 2,400 treated with interferon and 490 untreated, were evaluated. The results showed a significant beneficial effect of IFN by reducing the incidence of HCC in treated patients, particularly in patients who achieved a SVR and also in those with normalized

ALT levels. In untreated patients, an increase in the incidence of HCC was observed in parallel with the degree of fibrosis, from an annual rate of 0.5% for patients with F0-F1 to 7.9% in those with F4. Interestingly, the effect of interferon in preventing HCC was more beneficial in patients with F2 or F3 than in patients with F4 (cirrhosis). The incidence of HCC in sustained virologic responders was 0.49%, while in non-responders it was 5.32%. Similar results were published by Ikeda et al.<sup>23</sup> from 1,643 patients of whom 1,191 had received interferon therapy. The incidence of HCC in treated patients was 7.6% after 10 years of follow-up, compared with 12.4% in untreated patients. Two European studies failed to show that interferon had a beneficial effect either on the development of HCC or on the survival of treated patients.<sup>24,25</sup> In contrast, Sefarty et al.<sup>26</sup> in a retrospective study of 103 patients with HCV cirrhosis performed in the US, observed a beneficial effect of interferon on the development of HCC and on survival during a follow-up of three and a half years.

There are various explanations for the differences in the results of these studies. First, in Japan, the SVR rate is higher than that observed in Europe and the US. Secondly, the incidence of HCC is much higher in Japan. Both factors make it easier to demonstrate the preventative effect of therapy. There are also important methodological questions. The majority of the studies are retrospective and non-randomized, and this introduces a bias in the selection of patients for therapy. Factors associated with a higher incidence of HCC and cirrhotic decompensation such as greater age, lower albumin levels, lower platelet counts and more advanced fibrosis are more frequent in the untreated control group, which further complicates the comparison of the results.

Cammá et al.<sup>27</sup> performed a meta-analysis with a total of 3,109 patients and 356 cases of HCC. In 13 of the 14 studies, interferon reduced the incidence of HCC with a statistical significance in 10 studies. Overall, the differential risk was -12.8 (CI -8.3-17.2) ( $p < 0.00001$ ) for patients treated with interferon. The effect of treatment was more beneficial in patients who achieved a sustained biochemical response and also in those who showed no cirrhosis in the liver biopsy.

Luckily, with the combination of pegylated interferon and ribavirin, the overall SVR is higher than 50%, particularly in patients with cirrhosis, where it is much more efficacious than the old standard interferon monotherapy.<sup>6,7</sup>

The question that remains to be unanswered is whether interferon monotherapy can be beneficial in non-responders with advanced fibrosis. Different studies show that patients who achieve a biochemical response with normalization of ALT levels, but without a virological response, seem to have a lower incidence of HCC during follow-up and this could be related to the suppression of fibrosis progression by interferon. If this assumption is

correct, the current stopping rule of discontinuation therapy in non-responders at week 12 should be revised in order to benefit a higher number of patients. Whether long-term maintenance therapy with pegylated interferon could be of additional benefit in clinical terms, due to its antifibrogenic effect, still needs to be clarified. The answer will probably be found when the three ongoing studies, HALT, COPILOT and EPIC<sup>3</sup> with interferon maintenance, are completed.

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